

help in according applicants' advance its full merit.

The Examiner bases his rejection upon prior art which describes compounds of the type of instant formula I. In these references the use of the compounds is predominantly agro-chemical. In this connection the closest prior art is WO 93/14002. This reference describes systemic use of compounds of the type of formula I against fleas on pets.

This means there are two different fields of use where the word "systemic" has to be considered.

In order to be systemic in a plant, a compound has to be distributed through the plant by its sap stream. To achieve this it has to be water soluble at least to a large extent. Furthermore it has to be stable against degrading enzymes and microorganisms in the plant and in the soil.

The compound is then taken up orally by the insect sucking the sap stream. Toxicity upon oral uptaking governs activity. From the compounds of formula I it is known that insects are more susceptible to them when they take up the active compounds orally than when they come into contact with the active compounds. Again this is easily explained by the strongly polar nature of these compounds which helps transport within the insect.

Though the compounds possess excellent systemic activity against sap sucking plant damaging insects, they possess much less activity against plant damaging insects on contact. To be active by contact, the compound would have to penetrate the insects' cuticula. For this purpose it would be better if the compounds were non-polar. As compounds of this type are very polar, it is not astonishing that their contact activity against insects is relatively low.

In order to be systemic in an animal, a compound has to be distributed by the blood stream. Here, too, the compound has to be water soluble, and again it has to be stable against metabolizing enzymes and microorganisms.

In contrast to these systemic applications, applicants have another field of use, that is the non-systemic use on the skin or pelt of an animal. Governing here is the contact activity on insects. It has already been established that these compounds are known to have weaknesses in contact activity. Nevertheless applicants' concept is based upon the mode of action where these types of compounds are known to be weak.

As already mentioned, applicants treat the skin or pelt of animals. The active compound there is susceptible to being washed off by rain, decomposed by UV-radiation, decomposed by the microflora of the skin.

Another item not yet touched is long-term activity. In order to be useful, e.g. against

fleas, a strong knock-down effect and residual activity for at least 4 weeks is needed. Activity for more than 4 weeks effectively breaks the life cycle of fleas by preventing reinfestation with fleas which develop from eggs dropped before treatment. The shortest life cycle of fleas is about 3 weeks. Though it could be longer, flea infestation is a problem when the life cycle is at its shortest.

The foregoing hopefully establishes that, although the task - killing of a flea - is easy, looking for a solution theoretically is complex.

In support of what has been outlined above, there are appended hereto studies reporting on the following work:

1. Effectivity of Imidacloprid and 3 other compounds against fleas on dogs upon oral application to the dog.
2. Effectivity of imidacloprid on skin and pelt of dogs against fleas.
3. Assessment of the use of Imidacloprid to prevent and treat flea infestation in cats.

Report (1) demonstrates that the compounds in question are systemically active when taken up by animals orally. But their long term action (about 7 days) is by far less than satisfactory. It requires constant treatment every 7 days for at least 4 weeks, a

compliance problem for the owner and the treated animal.

Report (2) demonstrates that the active compound Imidacloprid when used in form of a spot-on formulation is distributed within 5 days all over the animal. Distribution is not the result of a systemic mode of action via passing through the skin, passing into blood circulation system, orally taken up by the blood sucking flea. This is proven by checking the effect upon fleas on differently treated types of skin. Nearly no effect upon fleas on skin-part which has been shaven and cleansed after treatment. Full effect on skin parts which have been shaven but not cleansed after treatment or which remained as they were after treatment.

Report (3) is the recommendation of the expert appointed by the UK registration authorities summarizing applicants' work with use of Imidacloprid against fleas on cats. Applicants have a similar report for use of Imidacloprid against fleas on dogs. This report is included to demonstrate that the inventive concept really works practically. These reports and their substance are included in the declaration of Dr. Dorn submitted herewith.

Turning now to the official action, the Examiner at page 4, line 1, notes that one reference says the pyridinylmethyl-imidazolidinium compounds are

"non-toxic to animals, fish, birds, etc."

From the foregoing explanation, to be useful for the purpose recited in the claims, much more than non-toxicity is required. There is durability over the life cycle of the fleas, contact activity, etc. Just safety will not mean effectiveness when used in contact. Non-toxicity is sort of "neutral". Much more is needed and is here provided.

Favorable action is solicited.

CONDITIONAL PETITION FOR EXTENSION OF TIME

If any extension of time for this response is required, applicants request that this be considered a petition therefor. Please charge the required petition fee to Deposit Account No. 02-1445.

ADDITIONAL FEE

Please charge any insufficiency of fees, or credit any excess, to Deposit Account No. 02-1445.

Respectfully submitted,
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